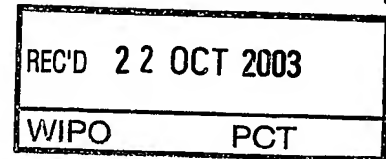


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RULE 17.1(a) OR (b)



Kongeriget Danmark

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Title: Novel raloxifene acid addition salts and/or solvates thereof, improved method for purification of said raloxifene acid addition salts/or solvates thereof and pharmaceutical compositions comprising these

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.



Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

15 July 2003

Pia Høybye-Olsen

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The invention relates to acid addition salts and/or solvates of [6-hydroxy-2-(4-hydroxyphenyl)benzol[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, raloxifene, capable of fast dissolution in media comprising hydrochloric acid, such as gastric juice. In addition useful crystal forms of the acid addition salts and/or solvates are disclosed.

In another aspect the invention relates to pharmaceutical composition for oral administration comprising said novel acid addition salts and/or solvates thereof, preferably in crystalline form. The pharmaceutical compositions according to the invention are useful because the high solubility in dilute hydrochloric acid, such as gastric juice secures a fast and reliable release of the active ingredient, raloxifene, in the stomach of the patient to whom said pharmaceutical composition have been administered.

Further the invention provides an improved method for preparation and purification of said acid addition salts and/or solvates thereof, which method provides for a quick and highly efficient purification of the crude raloxifene product.

20 **Background for the invention**

Raloxifene, [6-hydroxy-2-(4-hydroxyphenyl)benzol[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, is a well known compound having antiestrogene and antiandrogene activity. Raloxifene or raloxifene hydrochloride has proved useful for the preparation of pharmaceutical compositions for the treatment of cancer, osteoporosis and cartilage degradation.

Raloxifene, [6-hydroxy-2-(4-hydroxyphenyl)benzol[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, is also known as 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo-[b]-thiophen. Other names for raloxifene may also be found in the literature.

EP 62 503 A1 discloses benzothiophene compounds and process for preparing them. The disclosed compounds have antiestrogenic and antiandrogenic activity. Pharmaceutical preparation comprising said benzothiophene compounds are described, which preparations are useful for the treatment of

cancers. A particular preferred compound is Raloxifene. Acid addition salts of the benzothiophene compounds with physiologically acceptable acids are also disclosed. As examples of physiologically acceptable acids are mentioned among others sulphuric acid, succinic acid and lactic acid.

5 In the manufacture of raloxifene the crude product in the reaction mixture was evaporated to dryness, redissolved and purified in several steps before the pure produce was recovered as a crude product that was further purified to provide the desired compound.

 The obtained free base was subsequent transformed into acid addition
10 salts using usual techniques.

 EP 584 952 discloses use of raloxifene or acid addition salts thereof for the treatment of osteoporosis. It is preferred to use a acid addition salt of raloxifene instead of raloxifene as a free base because the acid addition salts generally have improved dissolution properties compared to the free base. As
15 examples of acids used for the acid addition salts are mentioned among others: hydrochloric acid, sulphuric acid, lactic acid, malonic acid and succinic acid. Raloxifene hydrochloride is the preferred acid addition salt.

 EP 652 002 A1 discloses use or 2-phenyl-3-arylbenzothiophenes or pharmaceutical acceptable acid addition salts thereof, such as raloxifene and
20 raloxifene hydrochloride respectively, for the inhibition of cartilage degradation.

 In WO 96/09045 raloxifene hydrochloride in crystalline form or as a solvate is described.

 EP 910 369 disclose raloxifene hydrochloride in crystal form where the crystals are smaller than 50 microns, and EP 826 682 disclose raloxifene
25 raloxifene in an amorphous form having enhanced solubility.

 At present most commercial available pharmaceutical compositions comprising raloxifene as active ingredient comprises raloxifene hydrochloride, because raloxifene hydrochloride is fairly soluble in aqueous solvents whereas raloxifene as free base is only sparingly soluble in aqueous solvents.

30 Despite the extensive experimentation of increasing the solubility of raloxifene there is still a need for providing the active compound in a form having increased availability of the active compound in order to provide pharmaceutical preparations for oral administration being fast soluble and thereby obtaining a fast and high bioavailability of the active compound raloxifene.

Brief description of the invention

The present invention relates to raloxifene acid addition salts and/or solvates thereof capable of fast and reliable dissolution in dilute hydrochloric acid.

The term fast dissolution is according to the invention intended to mean that the raloxifene salts and/or solvates thereof are dissolved faster than raloxifene. The term "reliable dissolution in dilute hydrochloric acid" is intended to mean that the dissolution does not strongly depend on the actual concentration of hydrochloric acid, and thereby will the availability of the raloxifene acid addition salts and/or solvates dissolve and make the active compound raloxifene available to the body rather independent on the conditions in the stomach which is known to vary during the day.

The present inventors have surprisingly discovered that the raloxifene acid addition salts and solvates according to the invention have improved dissolution properties in the presence of hydrochloric acid such as in gastric juice, compared with the commonly used raloxifene acid addition salt, raloxifene hydrochloride.

In a further aspect the invention relates to new and particular useful crystal forms of said novel raloxifene acid addition salts or solvates thereof.

In an even further aspect the invention relates to pharmaceutical compositions comprising said novel raloxifene acid addition salts and solvates thereof, which compositions are capable of fast and reliable dissolution in gastric juice.

Short description of the figures

Figure 1 shows a differential scanning calorimetric chart (DSC) for raloxifene DL-lactate hemihydrate. The chart was recorded at a rate of 20°C/min.

Figure 2 shows the X-ray diffraction pattern for crystalline raloxifene DL-lactate hemihydrate.

Figure 3 shows a DSC for raloxifene L-lactate hemihydrate. The chart was recorded at a rate of 20°C/min.

Figure 4 shows the X-ray diffraction pattern for crystalline raloxifene L-lactate hemihydrate.

5 Figure 5 shows a DSC for raloxifene L-lactate ¼-hydrate. The chart was recorded at a rate of 20°C/min.

Figure 6 shows the X-ray diffraction pattern for crystalline raloxifene L-lactate ¼-hydrate.

10

Detailed description of the invention

The inventors have realized that even though raloxifene hydrochloride is fairly soluble in aqueous media the solubility appear to decreases significant
15 in aqueous media comprising hydrochloric acid.

The skilled person will appreciate that gastric juice contains hydrochloric acid. Further the skilled person will appreciate that the composition of gastric juice apart from individual variations depends on various factors such as time of day, time since last meal and size and composition of said last meal.
20 However for the purpose of the present description, the gastric juice can be regarded as a dilute solution of hydrochloric acid having a pH value in the range of approximately 1-5, possible also containing sodium chloride in an amount of 1-3 % w/w.

Further the skilled person will know that the composition of the gastric
25 juice in an individual varies during the day, and consequently the uptake rate for a compound whose solubility depends on the concentration of hydrochloric acid in the gastric juice will also vary.

In contrast the inventors have surprisingly discovered that acid addition salts and/or solvates thereof according to the invention appear to be easy and
30 complete soluble less dependently of the concentration of hydrochloric acid than raloxifene as free base or raloxifene hydrochloride in crystalline or amorph form. Consequently, pharmaceutical preparations for oral administration comprising acid addition salts and /or solvates thereof according to the invention will provide the active compound raloxifene faster compared with pharmaceutical

preparations comprising raloxifene hydrochloride or raloxifene as free base.

Thus in one aspect the invention provides pharmaceutical preparations for oral administration comprising a raloxifene acid addition salt and/or solvate thereof as the active ingredient said preparations being capable of fast and complete dissolution in the stomach.

The fast and complete dissolution of the active compound secures that a therapeutic regimen using the pharmaceutical preparations according to the invention may be performed with higher accuracy because the attending physician will know that the complete dose will be available for assimilation in the gastrointestinal tract soon after the ingestion the pharmaceutical preparations according to the invention.

The dissolution of the raloxifene acid addition salts and/or solvates thereof according to the invention is not strongly dependent on hydrochloric acid in physiological concentrations. Therefore pharmaceutical compositions comprising such compounds will provide a faster and more reliable dissolution in the stomach and consequently a faster and more reliable uptake of said compounds by the individuals to whom said compositions are administered, compared with corresponding pharmaceutical compositions based on raloxifene or raloxifene hydrochloride.

Thus the pharmaceutical preparations according to the invention provide a fast and high availability of the active compound in the stomach soon after intake of the preparation.

Therefore in one aspect the present invention relates to pharmaceutical compositions for oral administration comprising raloxifene acid addition salts and/or solvates thereof, having fast and high bioavailability of the active compound raloxifene.

According to the invention the acid addition salts and/or solvates of raloxifene is selected among the succinate, lactate, malonate or the sulphate.

The lactate may be in the D or L form or a mixture thereof such as racemic mixtures. Further the lactate may be isolated as a solvate.

Because succinic acid, malonic acid and sulphuric acid have two acid groups per molecule, compounds of these acids and raloxifene may be isolated as either mono or di acid addition salts and/or solvates thereof having either one or two raloxifene molecules per acid molecule respectively.

In a preferred embodiment the acid addition salt and/or solvates thereof according to the invention is raloxifene DL-lactate, and in a particular preferred embodiment the acid addition salt is raloxifene L-lactate.

The skilled person will appreciate that the acid addition salts according to the invention may be isolated as solvates, which in the present description is to be understood as compounds where solvate molecules are included in the solid compounds, usually in defined stoichiometric amounts.

For some compounds more than one solvate may be isolated, which solvates differ only with respect of the solvent incorporated in the solid and the number of solvate molecules per molecule of the acid addition salt.

Preferred solvates according to the invention are solvates with pharmaceutically acceptable solvents such as water or alcohols having less than 5 carbon atoms, even more preferred selected among water, methanol, ethanol, propanol and 2-propanol.

Examples of solvates according to the invention include raloxifene L-lactate hemihydrate, raloxifene D-lactate hemihydrate, raloxifene DL-lactate hemihydrate, raloxifene L-lactate $\frac{1}{4}$ -hydrate, raloxifene D-lactate $\frac{1}{4}$ -hydrate, raloxifene DL-lactate $\frac{1}{4}$ -hydrate and raloxifene sulphate (2-propanol solvate).

Preferred compounds according to the invention include raloxifene D-lactate hemihydrate, raloxifene DL-lactate hemihydrate, raloxifene L-lactate hemihydrate and raloxifene L-lactate $\frac{1}{4}$ -hydrate, where raloxifene L-lactate hemihydrate and raloxifene L-lactate $\frac{1}{4}$ -hydrate is particular preferred.

It is well known that organic compounds may be isolated in crystalline form or in amorph form. Generally it is preferred to provide compounds in crystalline form because crystallisation usually is accompanied by a purification of the compound, and further, because crystals are more well defined solids than amorph materials the properties of compounds in crystalline form varies less than materials in amorph form.

Therefore the raloxifene acid addition salts and/or solvates according to the invention in crystalline form provides another aspect of the invention.

The raloxifene acid addition salts in crystalline form according to the

invention are raloxifene lactate, raloxifene malonate and raloxifene succinate, which all exist as distinct crystalline compounds, and raloxifene sulphate, which may be isolated in crystalline form as a 2-propanol solvate having one molecule of 2-propanol incorporated per two raloxifene molecules.

5 For some of the raloxifene acid addition salts and/or solvates thereof according to the invention more than one crystal form may be possible, where the different crystal forms may be prepared dependent on the solvent, temperature etc, as it will be known within the area.

10 Pharmaceutical preparations for oral administration comprising raloxifene salts and /or solvates thereof according to the invention may be prepared using pharmaceutical techniques well known within the area e.g. from text books such as Remington's manual.

15 For example may the raloxifene compounds according to the invention be formed for oral administration into tablets, capsules etc. In forming the pharmaceutical preparations the compounds according to the invention may be mixed with usual fillers and excipients, such as disintegration agents, lubricants, swelling agents. The preparations may also be coated according to well-known techniques.

20

Raloxifene acid addition salts and/or solvates may be prepared using methods known for the skilled person.

25 For example may any acid addition salt be converted into the free base and subsequently the free base may be converted into another acid addition salt by known procedures.

Usually raloxifene is prepared directly as raloxifene hydrochloride.

30 The present inventors have observed that in contrast to raloxifene and previously tested acid addition salts thereof e.g. raloxifene hydrochloride, can raloxifene lactate easily be crystallized in high yield and high purity from an alcoholic solution.

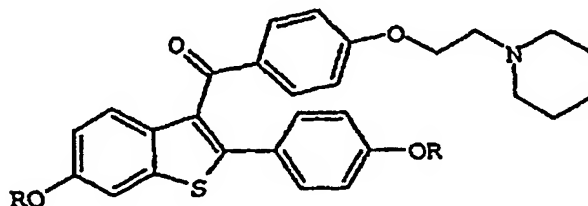
It has been realized that this property may be used for a quick and high efficient purification of raloxifene lactate from an intermediate in the synthesis of raloxifene.

Thus raloxifene lactate may be prepared directly without previous isolation of free raloxifene or raloxifene hydrochloride using the following procedure:

To a solution of the compound having the general formula I

5

10



Formula I

wherein R represent two independently selected hydroxyl protection groups,

in a solvent is added a suitable reagent to remove the protection groups. Next the pH of the mixture is adjusted to neutral reaction using lactic acid, whereafter raloxifene lactate may be precipitated and isolated.

This procedure according to the invention is beneficial because raloxifene lactate is easily crystallized from such a mixture, particular if the solvent is an alcohol having 1-5 carbon atoms. The easy crystallisation of raloxifene lactate represents a high and easy purification of the raloxifene from the reaction mixture. The crystallized raloxifene lactate may be further purified by recrystallization from an alcohol.

The compound having the formula I is known within the art from e.g. EP 875 511 A1, where it is called formula VII, and from EP 62 503, where it is prepared by the reaction scheme (B).

The group R may be any hydroxyl protection group known to the skilled person. For example may R be selected from C₁-C₄ alkyl, C₃-C₇ cycloalkyl, benzyl -COR² or SO₂R², wherein R² is C₁-C₄ primary or secondary alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ chloroalkyl, C₁-C₄ alkylphenyl, C₁-C₄ alkoxyphenyl, mono- or dinitrophenyl or mono- or di(chloro or fluoro)phenyl.

The two R groups may be the same or different. It is preferred that the two R groups are selected so that the similar conditions are needed to remove

the two groups.

The term "neutral reaction" is intended to mean that the mixture has a pH value in the range of 6-8, preferably 7.0-7.5.

5 The chemical used to remove the protection groups may be any chemical known to be able to remove the particular used protection groups. It is within the skills of the practitioner to select a suitable chemical to remove the protection group for each selected protection group.

10 The solvent used for the reaction may in principle be any solvent that can dissolve the reagents and does not participate in reactions with any of the ingredients of the reaction mixture under the conditions applied. Preferred solvents are alcohols having 1 to 5 carbon atoms. Particular preferred solvents are monovalent alcohols having 1 to 5 carbon atoms, where methanol, ethanol, propanol and 2-propanol are the most preferred solvents.

15 The obtained raloxifene lactate may be recrystallized in order to obtain the compound in even higher purity.

As solvent for the crystallization may in principle be used any alcohol having suitable melting and boiling temperatures. Alcohols having 1 to 5 carbon atoms and one hydroxyl group are preferred.

20 As examples of preferred alcohols can be mentioned methanol, ethanol, propanol, 2-propanol, butanol, 2-butanol, neobutyl alcohol, pentanol, 2-pentanol and 3-pentanol.

It is within the abilities of the skilled practitioner to select a suitable solvent for crystallization of particular selected compound of the invention.

25 Ethanol is a particular preferred alcohol.

The concentration of alcohol in the crystallization mixture should be higher than 90%, preferably higher than 95%.

A particular preferred solvent for the crystallisation reaction is 96% ethanol.

30 The crystallisation may be performed using procedures known within the area. Further as it will be known for the skilled person it may be advantageous to add seeding crystals to the crystallization mixture to promote crystallisation.

Thus in another aspect the invention relates to a method for purification of raloxifene lactate from a alcoholic solution of raloxifene comprising addition of lactate, adjusting pH and temperature of the obtained mixture and isolation of the formed crystalline raloxifene lactate.

5 In a preferred embodiment the alcoholic solution of raloxifene is the reaction mixture of the synthesis of raloxifene if necessary after a change of solvent.

The invention is further illustrated by way of examples, which are
10 solely provided for illustration and should not be considered as limiting in any way.

EXAMPLES

15

Example 1

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, succinate; Raloxifene succinate.

20 37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep
25 red solution appears. Reminiscence of insoluble product may be filtered off.

1 L of a solution of 70.85 g (0.6 mol) succinic acid in 2-propanol/water (80:20) is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-
30 propanol and then dried in vacuo at 55-65 °C for 16 hours to give 178.5 g crude product.

The crude product is stirred with 890 ml of water for 3 hours and then filtered off and washed 3 times with 100 ml of water. The product is dried in vacuo at 55-65 °C for 16 hours to give 89.7 g (77.3% yield) of product.

Mp: dec. > 195 °C, mp. ~ 225 °C

Elemental analysis $C_{33}H_{33}NO_8S$:

5 Calculated: C: 64.96% H: 5.62% N: 2.37% S: 5.42%

Found: C: 65.64% H: 5.49% N: 2.60% S: 5.99%

IR:

3406 cm^{-1} , 3145 cm^{-1} , 2945, 2691 cm^{-1} , 1642 cm^{-1} , 1597 cm^{-1} , 1541 cm^{-1} ,
 10 1501 cm^{-1} , 1457 cm^{-1} , 1430 cm^{-1} , 1421 cm^{-1} , 1356 cm^{-1} , 1259 cm^{-1} , 1234 cm^{-1} ,
 1171 cm^{-1} , 1125 cm^{-1} , 1108 cm^{-1} , 1079 cm^{-1} , 1047 cm^{-1} , 1038 cm^{-1} , 907
 cm^{-1} , 839 cm^{-1} , 807 cm^{-1} , 623 cm^{-1}

XRD:

15

	D	2Theta	I(rel)	I(abs)	FWHM
	13.195230	6.6933	20.78	8475	0.1400
	9.695642	9.1137	13.43	5476	0.0300
20	9.304945	9.4972	18.19	7419	0.1300
	8.394523	10.5300	13.26	5407	0.1000
	7.944460	11.1283	14.15	5768	0.1000
	7.708667	11.4699	17.61	7180	0.1200
	7.526675	11.7482	12.32	5023	0.0898
25	7.323294	12.0756	15.22	6205	0.1000
	7.160495	12.3512	13.04	5316	0.0800
	6.926815	12.7696	23.68	9655	0.1300
	6.606409	13.3917	29.08	11856	0.1400
	6.463392	13.3894	14.45	5891	0.0898
30	6.285432	14.0789	21.24	8662	0.1200
	6.127742	14.4432	63.63	25947	0.1200
	5.961999	14.8469	15.55	6342	0.0900
	5.875574	15.0665	15.77	6430	0.0898
	5.788967	15.2933	16.15	6585	0.1400

	5.624221	15.7441	34.74	14167	0.1200
	5.453763	16.2394	22.89	9334	0.1300
	5.276560	16.7887	12.71	5182	0.1200
	5.095057	17.3913	14.19	5786	0.1100
5	5.020392	17.6520	11.12	4535	0.0898
	4.835944	18.3309	18.30	7461	0.1200
	4.765096	18.6059	18.62	7591	0.1100
	4.630456	19.1519	65.88	26864	0.1600
	4.525518	19.6003	15.16	6180	0.0800
10	4.484997	19.7792	24.48	9982	0.1000
	4.376528	20.2745	18.78	7659	0.1000
	4.352225	20.3889	19.11	7790	0.1000
	4.227757	20.9959	29.39	11984	0.1000
	4.191265	21.1808	56.82	23171	0.0800
15	4.158052	21.3520	40.16	16377	0.0898
	4.101947	21.6475	17.14	6988	0.0800
	4.062068	21.8626	19.79	8072	0.1000
	4.010082	22.1496	11.70	4771	0.0600
	3.921660	22.6556	100.00	40776	0.1300
20	3.860487	23.0194	29.04	11842	0.1100
	3.813566	23.3066	19.25	7850	0.1100
	3.732687	23.8189	19.33	7884	0.1300
	3.694791	24.0669	22.47	9161	0.1100
	3.644300	24.4054	18.84	7680	0.1400
25	3.544078	25.1067	13.63	5556	0.0700
	3.496160	25.4565	16.28	6637	0.0898
	3.446458	25.8299	20.36	8300	0.2100
	3.398344	26.2021	12.35	5036	0.1200
	3.373032	26.4022	8.82	3597	0.0898
30	3.305938	26.9481	14.08	5741	0.1100
	3.281940	27.1489	10.08	4112	0.0898
	3.260437	27.3314	9.66	3937	0.0898
	3.227083	27.6194	19.22	7838	0.1200
	3.179256	28.0434	16.28	6640	0.2600

	3.146269	28.3435	8.89	3627	0.0898
	3.121159	28.5764	9.58	3907	0.0900
	3.097691	28.7975	10.64	4337	0.0400
	3.074307	29.0213	19.64	8008	0.1200
5	3.032262	29.4328	10.17	4148	0.1300
	3.010128	29.6541	9.43	3847	0.0898

Example 2

10

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, malonate; Raloxifene malonate.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250
 15 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

20 260 ml of a solution of 62.76 g (0.6 mol) malonic acid in 2-propanol/water is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 182.4g crude
 25 product.

The crude product is stirred with 912 ml of water for 3 hours and then filtered off and dried in vacuo at 55-65 °C for 16 hours to give 98.7g (87.2% yield) of crude product. The crude product is boiled for 5 minutes in 500 ml 2-propanol and then cooled at 10 °C for 30 minutes. The product is filtered off and washed
 30 with 100 ml 2-propanol and then dried in vacuo to give 90.8g (97%) of the product.

Mp: . 226-227 °C

Elemental analysis C₃₂H₃₁NO₈S:**Calculated:** C: 64.46% H: 5.41% N: 2.42% S: 5.55%**Found:** C: 64.86% H: 5.55% N: 2.57% S: 5.87%

5

IR:

3388 cm⁻¹, 3199 cm⁻¹, 2950 cm⁻¹, 2683 cm⁻¹, 2543 cm⁻¹, 1643 cm⁻¹, 1597 cm⁻¹,
 1539 cm⁻¹, 1502 cm⁻¹, 1467 cm⁻¹, 1421 cm⁻¹, 1355 cm⁻¹, 1306 cm⁻¹, 1255
 cm⁻¹, 1169 cm⁻¹, 1038 cm⁻¹, 952 cm⁻¹, 907 cm⁻¹, 839 cm⁻¹, 808 cm⁻¹, 645
 10 cm⁻¹, cm⁻¹, 623 cm⁻¹

XRD:

	D	2Theta	I(rel)	I(abs)	FWHM
15	14.385166	6.1391	36.51	6471	0.0100
	13.125024	6.7292	38.91	6896	0.1300
	10.305386	8.5734	37.32	6614	0.1700
	9.279238	9.5236	39.85	7062	0.1300
20	8.860721	9.9745	34.60	6133	0.0900
	8.510328	10.3863	33.27	5895	0.0900
	8.314361	10.6318	33.02	5852	0.0800
	7.947949	11.1234	41.61	7375	0.1600
	7.265135	12.1727	35.79	6343	0.1300
25	6.882996	12.8512	29.65	5254	0.0300
	6.537915	13.5326	60.19	10667	0.1800
	6.258251	14.1404	61.12	10833	0.2100
	6.003203	14.7444	31.92	5657	0.1200
	5.877911	15.0605	29.17	5170	0.0600
30	5.794580	15.2784	29.33	5198	0.0200
	5.663226	15.6349	49.63	8796	0.1300
	5.550457	15.9547	36.61	6487	0.0800
	5.354103	16.5438	55.84	9897	0.2200
	5.134028	17.2583	30.18	5349	0.1378

	5.023848	17.6397	55.21	9784	0.2100
	4.836637	18.3283	36.13	6404	0.1400
	4.700761	18.8628	71.64	12696	0.1600
	4.644808	19.0922	86.46	15323	0.1500
5	4.538522	19.5436	61.36	10874	0.1300
	4.472256	19.8361	50.40	8931	0.1000
	4.347111	20.4132	37.86	6709	0.1000
	4.247918	20.8951	88.12	15616	0.2300
	4.161428	21.3344	73.93	13101	0.1600
10	4.085803	21.7341	37.19	6591	0.1100
	4.019584	22.0966	35.60	6309	0.1500
	3.921695	22.6554	100.00	17722	0.1700
	3.765729	23.6059	50.70	8986	0.2000
	3.703455	24.0097	34.79	6166	0.1200
15	3.638542	24.4446	47.30	8382	0.1900
	3.499221	25.4339	44.29	7849	0.2000
	3.426872	25.9801	43.63	7732	0.2200
	3.292398	27.0610	23.39	4145	0.1000
	3.253755	27.3886	25.03	4435	0.1400
20	3.192249	27.9269	22.18	3931	0.1400
	3.094846	28.8246	28.68	5083	0.3000
	3.034329	29.4123	27.30	4338	0.1900

25

Example 3

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, sulfate (2-propanol solvat); Raloxifene sulfate
(2-propanol solvat).

30

3.79g (~0.06 mol) pulverized potassium hydroxide (>85%) is dissolved in 125 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30

minutes. 10g (0.0196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

- 5 A solution of 6.5g 96% (0.6 mol) sulphuric acid in 15 ml 2-propanol and 12 ml of water is added with violent stirring during 1-1.5 hours (weakly exothermic). The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white crystals. The product is now washed 2 times with 4 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 15g
10 crude product.

- The crude product is stirred with 76 ml of water for 3 hours and then filtered off and washed 3 times with 100 ml of water. The product is dried in vacuo at 55-65 °C for 16 hours to give 8.6g (% yield) of product. The product is boiled with 38 ml of 2-propanol for 5 minutes and then cooled on to 0-5°C for 30 minutes and
15 filtered. The product is washed with 2 times with 5 ml 2-propanol, and dried in vacuum at 70-75 °C.

Mp: . 262-263 °C

20 **Elemental analysis $C_{59}H_{64}N_2O_{13}S_3$:**

Calculated: C: 64.46% H: 5.41% N: 2.42% S: 5.55%

Found: C: 64.86% H: 5.55% N: 2.57% S: 5.87%

IR:

- 25 3199 cm^{-1} , 2963 cm^{-1} , 2723 cm^{-1} , 2693 cm^{-1} , 2659 cm^{-1} , 2559 cm^{-1} , 1653 cm^{-1} , 1597 cm^{-1} , 1547 cm^{-1} , 1501 cm^{-1} , 1467 cm^{-1} , 1437 cm^{-1} , 1419 cm^{-1} , 1344 cm^{-1} , 1308 cm^{-1} , 1268 cm^{-1} , 1251 cm^{-1} , 1233 cm^{-1} , 1167 cm^{-1} , 1037 cm^{-1} , 1020 cm^{-1} , 952 cm^{-1} , 907 cm^{-1} , 839 cm^{-1} , 823 cm^{-1} , 809 cm^{-1} , 627 cm^{-1} , 524 cm^{-1} .

XRD:

	D	2Theta	I(rel)	I(abs)	FWHM
5	14.374007	6.1439	26.57	5009	0.0900
	10.303750	8.5748	29.62	5583	0.1300
	9.201529	9.6042	26.22	4942	0.1100
10	8.871726	9.9621	29.84	5624	0.1300
	8.569965	10.3138	22.25	4195	0.0400
	8.320378	10.6241	25.97	4896	0.1200
	7.945119	11.1274	38.65	7286	0.1300
	7.514174	11.7678	20.56	3876	0.1041
15	7.205108	12.2745	25.04	4721	0.1400
	6.537437	13.5336	66.78	12590	0.1400
	6.228787	14.2076	21.88	4126	0.1100
	5.628329	15.7325	20.71	3904	0.0900
	5.540447	15.9837	27.40	5166	0.1100
20	5.322476	16.5489	64.98	12249	0.1500
	5.138694	17.2425	21.65	4082	0.1100
	5.020317	17.6522	64.05	12074	0.1400
	4.706881	18.8381	100.00	18851	0.1300
	4.618097	19.2036	60.47	11400	0.0800
25	4.538129	19.5453	59.35	11189	0.1100
	4.471816	19.8381	67.03	12636	0.1200
	4.261964	20.8255	54.78	10327	0.1100
	4.204757	21.1121	51.35	9680	0.1600
	4.156029	21.3625	46.65	8794	0.1041
30	4.093305	21.6938	25.93	4888	0.0900
	4.035960	22.0058	24.21	4563	0.1800
	3.937182	22.5651	25.37	4784	0.1200
	3.835400	23.1721	22.17	4179	0.0900
	3.796528	23.4127	40.94	7718	0.0900

	3.767170	23.5978	61.03	11505	0.1100
	3.691303	24.0899	20.10	3790	0.1500
	3.639317	24.4393	47.20	8897	0.1200
	3.590489	24.7769	28.23	5321	0.1600
5	3.511060	25.3467	29.66	5592	0.1100
	3.478586	25.5873	23.70	4468	0.1041
	3.416539	26.0601	37.38	7047	0.1900
	3.355389	26.5436	20.28	3823	0.1300
	3.314637	26.8760	17.08	3220	0.1200
10	3.271015	27.2413	15.24	2874	0.0600
	3.252583	27.3987	14.71	2773	0.1041
	3.100446	28.7714	23.04	4344	0.1200
	3.079703	28.9694	19.73	3720	0.1041
	3.033828	29.4172	29.23	5511	0.1300
15	3.009744	29.6580	15.28	2880	0.1041
	2.937725	30.4024	13.30	2507	0.1700

20 Exemple 4

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, DL-lactate hemihydrate; Raloxifene DL-lactate hemihydrate.

25

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

30

A solution of 67.6 g 85% DL-lactic acid (0.6 mol) in 200 ml of 2-propanol is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as

white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 109 g crude product.

The crude product is stirred with 545 ml of water for 3 hours and then filtered off and washed 2 times with 75 ml of water. The product is dried in vacuo at 75-80 °C for 16 hours to give 92.7g (83.9% yield) of product.

Mp: . 196-198 °C

10 Elemental analysis $C_{34}H_{33}NO_7S (\frac{1}{2}H_2O)$:

Calculated: C: 65.00 % H: 5.98 % N: 2.45 % S: 5.60 %

Found: C: 65.07% H: 5.93 % N: 2.37 % S: 5.34 %

IR:

15 3385 cm^{-1} , 3223 cm^{-1} , 2940 cm^{-1} , 2675 cm^{-1} , 1641 cm^{-1} , 1598 cm^{-1} , 1542 cm^{-1} , 1502 cm^{-1} , 1467 cm^{-1} , 1421 cm^{-1} , 1349 cm^{-1} , 1307 cm^{-1} , 1253 cm^{-1} , 1171 cm^{-1} , 1123 cm^{-1} , 1038 cm^{-1} , 953 cm^{-1} , 908 cm^{-1} , 837 cm^{-1} , 808 cm^{-1} , 649 cm^{-1} , 623 cm^{-1} , cm^{-1} , 532 cm^{-1} , 514 cm^{-1} .

20 The product was further analysed using differential scanning calorimetry using a METTLER TOLEDO STAR® system, according to the instructions of the manufacturer. The differential scanning calorimetric chart (DSC) is shown in figure 1.

25 Further the product was analysed by X-ray diffraction analysis using the STOE Powder diffraction system. The result is shown in figure 2, and is also listed numerically below.

30 XRD:

<u>D</u>	<u>2Theta</u>	<u>I(rel)</u>	<u>I(abs)</u>	<u>FWHM</u>
13.595814	6.4959	28.40	12683	0.1400

	10.855533	8.1382	16.15	7211	0.1200
	9.849394	8.9711	32.17	14369	0.1000
	9.534325	9.2682	66.95	29898	0.1300
	8.150249	10.8465	45.20	20188	0.1300
5	7.240730	12.2138	63.53	28374	0.1400
	6.769843	13.0670	18.42	8227	0.1500
	6.272666	14.1077	75.67	33794	0.1900
	5.818832	15.2143	13.28	5933	0.2000
	5.657337	15.6513	18.07	8070	0.1300
10	5.505030	16.0872	10.51	4692	0.1000
	5.261933	16.8357	17.48	7806	0.1400
	5.089504	17.4104	16.14	7210	0.1000
	5.001569	17.7189	41.94	18732	0.0900
	4.958950	17.8725	29.16	13023	0.1148
15	4.797388	18.4795	19.39	8660	0.1100
	4.669322	18.9910	49.20	21972	0.1400
	4.574684	19.3876	63.21	28227	0.1000
	4.533019	19.5676	44.94	20071	0.1148
	4.440548	19.9792	32.70	14604	0.1200
20	4.301886	20.6301	100.00	44659	0.1500
	4.155406	21.3657	78.00	34833	0.1600
	4.059049	21.8797	27.53	12296	0.1800
	3.960846	22.4285	25.59	11427	0.1000
	3.907408	22.7393	83.48	37282	0.1200
25	3.865461	22.9894	16.46	7350	0.1148
	3.828892	23.2120	17.46	7798	0.0900
	3.773130	23.5599	50.71	22649	0.1200
	3.716486	23.9243	23.06	10300	0.1300
	3.652238	24.3515	15.79	7053	0.1800
30	3.584725	24.8174	12.91	5764	0.1500
	3.486791	25.5261	30.45	13600	0.1200
	3.439149	25.8858	22.21	9919	0.1300
	3.396267	26.2184	17.86	7978	0.1100
	3.370045	26.4261	12.48	5572	0.1148

	3.329320	26.7553	9.21	4113	0.1100
	3.292728	27.0582	11.81	5274	0.1000
	3.278070	27.1815	11.25	5026	0.1148
	3.218620	27.6935	21.24	9485	0.1900
5	3.167986	28.1452	13.80	6162	0.0900
	3.143230	28.3715	30.33	13546	0.1000
	3.095423	28.9191	14.02	6260	0.1200
	3.024921	29.5058	11.56	5161	0.1400
	3.007253	29.6831	13.40	5984	0.1300
10					

Example 5

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, L-lactate hemihydrate; Raloxifene L-lactate hemihydrate.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

A solution of 67.6 g 85% L-lactic acid (0.6 mol) is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 109 g crude product.

The crude product is stirred with 545 ml of water for 3 hours and then filtered off and washed 2 times with 75 ml of water. The product is dried in vacuo at 75-80 °C for 16 hours to give 92.7g (83.9% yield) of product.

Mp: . 134-136°C

Elemental analysis C₃₁H₃₃NO₇S (½H₂O):

Calculated: C: 65.00 % H: 5.98 % N: 2.45 % S: 5.60 %

Found: C: 65.08% H: 6.14 % N: 2.58 % S: 5.78 %

5 IR:

3167 cm⁻¹, 2934 cm⁻¹, 1641 cm⁻¹, 1627 cm⁻¹, 1593 cm⁻¹, 1543 cm⁻¹, 1500 cm⁻¹, 1469 cm⁻¹, 1433 cm⁻¹, 1350 cm⁻¹, 1314 cm⁻¹, 1259 cm⁻¹, 1170 cm⁻¹, 1128 cm⁻¹, 1103 cm⁻¹, 1033 cm⁻¹, 908 cm⁻¹, 836 cm⁻¹, 809 cm⁻¹.

10

The product was analysed using differential scanning calorimetry using a METTLER TOLEDO STAR® system, according to the instructions of the manufacturer. The differential scanning calorimetric chart (DSC) is shown in figure 3.

15

Further the product was analysed by X-ray diffraction analysis using the STOE Powder diffraction system. The result is shown in figure 4, and is also listed numerically below.

20

XRD:

	D	2Theta	I(rel)	I(abs)	FWHM
25	14.639874	6.0322	17.56	6122	0.1200
	13.207421	6.6871	15.07	5254	0.1200
	10.875932	8.1229	80.41	28029	0.1200
	9.268456	9.5347	22.67	7903	0.1200
	8.140638	10.8593	17.92	6247	0.1200
30	7.488503	11.8083	15.59	5433	0.1000
	7.310331	12.0971	12.47	4347	0.0800
	7.089508	12.4754	25.79	8991	0.1000
	6.931874	12.7603	12.78	4454	0.0900
	6.723932	13.1566	27.83	9701	0.1300

	6.551458	13.5045	14.20	4949	0.0900
	6.359432	13.9143	30.57	10656	0.1100
	6.130010	14.4378	21.33	7435	0.1300
	5.853018	15.1249	36.40	12687	0.1100
5	5.626204	15.7385	15.49	5401	0.1300
	5.507643	16.0795	23.25	8106	0.1000
	5.447238	16.2590	13.21	4606	0.0870
	5.224449	16.9573	19.21	6697	0.1100
	5.160516	17.1690	17.10	5961	0.0870
10	5.083475	17.4312	14.74	5137	0.1100
	4.954247	17.8896	19.64	6848	0.1000
	4.863750	18.2252	28.34	9879	0.0800
	4.805168	18.4494	46.26	16125	0.0700
	4.756883	18.6383	49.99	17425	0.0800
15	4.656926	19.0420	19.10	6659	0.1900
	4.630194	19.1530	17.96	6260	0.0870
	4.566015	19.4248	21.34	7438	0.1000
	4.487514	19.7680	12.76	4447	0.1000
	4.347753	20.4101	11.69	4074	0.1100
20	4.301465	20.6322	19.17	6682	0.0900
	4.224555	21.0120	14.55	5072	0.0870
	4.186561	21.2049	23.33	8134	0.1700
	4.065767	21.8425	26.06	9084	0.1000
	4.015560	22.1190	17.10	5929	0.1000
25	3.976949	22.3365	14.98	5223	0.0500
	3.935785	22.5732	34.50	12028	0.1100
	3.867038	22.9799	100.00	34859	0.1000
	3.779481	23.5198	40.14	13991	0.0800
	3.742319	23.7567	59.68	20805	0.1000
30	3.710418	23.9640	13.17	4591	0.0870
	3.645564	24.3968	11.19	3902	0.0800
	3.621808	24.5593	18.71	6524	0.1000
	3.552536	25.0459	16.01	5581	0.1000
	3.516088	25.3098	13.46	4691	0.0600

	3.498357	25.4402	12.66	4413	0.0700
	3.467075	25.6737	10.74	3745	0.0500
	3.418947	26.0414	21.49	7491	0.1000
	3.395298	26.2260	12.12	4225	0.0870
5	3.369948	26.4268	15.48	5369	0.0700
	3.358554	26.5181	14.33	4995	0.0600
	3.244985	27.4641	11.90	4149	0.0700
	3.229427	27.5990	9.63	3356	0.0870
	3.177657	28.0578	15.07	5253	0.1200
10	3.144884	28.3562	32.65	11381	0.1000
	3.106130	28.7176	9.83	3425	0.0800
	3.082970	28.9380	9.00	3138	0.0870
	3.056106	29.1980	8.56	2984	0.0870
	3.032184	29.4335	8.74	3048	0.1100
15	2.994539	29.8121	8.27	2884	0.0700
	2.979114	29.9700	9.26	3229	0.0800
	2.924922	30.5387	9.19	3203	0.1800
	2.870290	31.1346	16.32	5689	0.1400
	2.828902	31.6019	13.59	4737	0.1100
20	2.762611	32.3808	10.83	3775	0.1000

Example 6

25 [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-]; Raloxifene L-lactate (1/4 H₂O).

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250
 30 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30
 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in
 such a way that temperature is kept below 30 °C. After addition of raloxifene
 hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep
 red solution appears. Reminiscence of insoluble product may be filtered off.

A solution of 67.6g 85% L-lactic acid (0.6 mol) is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours. If no or very little precipitate appears in the solution the reaction mixture is filtered and 2-propanol is evaporated off. To the reminsce is now added
 5 150 ml of water with stirring and the precipitated product is collected by filtration and dried in vacuo at 55-65°C. Next the crude product is recrystallized from 160 ml 96% ethanol (if necessary seeding crystals are added) to give 62.8g (56.4%) of the product.

10 **Mp:** 171-173 °C :

Elemental analysis $C_{31}H_{33}NO_7S$ (1/4H₂O):

Calculated: C: 65.52 % H: 5.94 % N: 2.47 % S: 5.64 %

15 **Found:** C: 65.50% H: 5.85 % N: 2.50 % S: 5.74 %

IR:

3159 cm⁻¹, 2935 cm⁻¹, 2806 cm⁻¹, 2672 cm⁻¹, 1643 cm⁻¹, 1598 cm⁻¹, 1574
 20 cm⁻¹, 1547 cm⁻¹, 1501 cm⁻¹, 1466 cm⁻¹, 1422 cm⁻¹, 1347 cm⁻¹, 1308 cm⁻¹,
 1269 cm⁻¹, 1229 cm⁻¹, 1171 cm⁻¹, 1119 cm⁻¹, 1067 cm⁻¹, 1037 cm⁻¹, 1006
 cm⁻¹, 908 cm⁻¹, 835 cm⁻¹, 807 cm⁻¹, 665 cm⁻¹,
 649 cm⁻¹, 634 cm⁻¹, 623 cm⁻¹, 513 cm⁻¹.

25

The product was analysed using differential scanning calorimetry using a METTLER TOLEDO STAR® system, according to the instructions of the manufacturer. The differential scanning calorimetric chart (DSC) is shown in figure 5.

30 Further the product was analysed by X-ray diffraction analysis using the STOE Powder diffraction system. The result is shown in figure 6, and is also listed numerically below.

XRD:

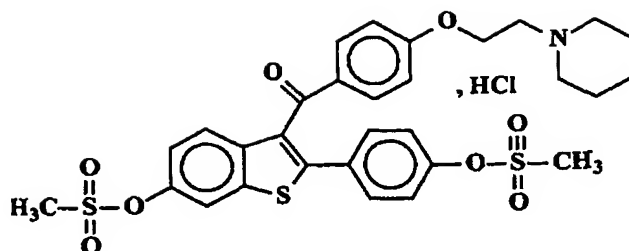
	D	2Theta	I(rel)	I(abs)	FWHM
5	14.079244	6.2726	45.93	16568	0.1300
	9.974912	8.8580	32.43	11699	0.1100
	9.526523	9.2758	71.31	25721	0.1200
10	8.215598	10.7600	47.82	17248	0.1100
	7.246270	12.2045	80.04	28871	0.1100
	7.065557	12.5178	16.17	5832	0.0700
	6.878001	12.8606	22.74	8201	0.1200
	6.283709	14.0828	66.27	23901	0.0800
15	6.194698	14.2862	53.98	19470	0.0984
	5.859529	15.1080	11.17	4028	0.0984
	5.744935	15.4112	16.16	5828	0.1200
	5.312222	16.6751	18.02	6499	0.1200
	5.046910	17.5585	34.26	12356	0.0900
20	4.978933	17.8001	54.66	19715	0.1000
	4.918535	18.0205	17.40	6277	0.0984
	4.746264	18.6804	26.77	9655	0.1000
	4.712771	18.8143	46.35	16716	0.0900
	4.569429	19.4101	57.60	20777	0.1000
25	4.455985	19.9093	53.60	19332	0.1200
	4.345589	20.4204	12.70	4579	0.0900
	4.268096	20.7952	86.33	31139	0.0900
	4.106332	21.6241	20.17	7274	0.1100
	4.042283	21.9710	22.73	8197	0.1200
30	3.944656	22.5218	23.46	8462	0.1000
	3.913129	22.7056	100.00	36069	0.1100
	3.831706	23.1947	15.49	5586	0.0900
	3.777075	23.5350	69.72	25148	0.1400
	3.735872	23.7983	14.85	5358	0.0984

	3.667856	24.2463	11.94	4305	0.0900
	3.639035	24.4413	13.87	5001	0.0800
	3.589918	24.7809	9.38	3383	0.0984
	3.545715	25.0949	23.58	8505	0.0800
5	3.505655	25.3864	33.63	12131	0.1100
	3.442223	25.8622	22.60	8152	0.1100
	3.411017	26.1030	10.82	3901	0.0984
	3.371851	26.4117	44.16	5108	0.1000
	3.280618	27.1600	15.23	5494	0.1100
10	3.251104	27.4114	14.23	5134	0.0800
	3.232072	27.5760	19.25	6943	0.1100
	3.153056	28.2812	12.42	4479	0.1900
	3.143130	28.3724	12.29	4432	0.0984
	3.081939	28.9479	17.16	6189	0.2200
15	3.040378	29.3524	9.73	3510	0.1300
	2.990508	29.8532	15.29	5514	0.1400
	2.929711	30.4876	11.37	4102	0.1200
	2.892397	30.8906	18.91	6822	0.1200
	2.856192	31.2922	8.91	3214	0.1100
20	2.818108	31.7261	14.79	5336	0.2500
	2.765584	32.3450	15.86	5720	0.1300

Example 7

25 Preparation of [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, L-lactate hemihydrate; Raloxifene L-lactate (1/4 H₂O).

40g (0.06 mol) 6-methylsulphonyloxy-2-(4-methylsulphonyl-
 30 oxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, hydrochlorid, having the structural formula below



is suspended in 385 ml 2-propanol. 21.75g (0.33 mol) powdered 85% potassium
 5 hydroxide is added with stirring, and the mixture is heated to reflux for 2 hour.
 The deep red solution is cooled to room temperature, and a solution of 20.3 g
 85% L-lactic acid (0.18 mol) is added with violent stirring during 1-1.5 hours,
 whereafter the 2-propanol is evaporated off to give the crude product. The prod-
 10 uct is recrystallized from approximately 50 ml 96% ethanol to give 16.6g (49.2
 %) of the pure product. Elemental analysis, melting point, IR and XRD are in
 accordance with example 6.

Example 8 (Comparative example)

15

Dissolution of raloxifene hydrochloride in dilute hydrochloric acid or phosphoric acid

60 mg raloxifene HCl was transferred to a dissolution vessel contain-
 20 ing one litre 0.1 M HCl. The mixture was vigorously mixed and left at room
 temperature over night. Subsequently the dissolution was evaluated visually.
 Very little of the initial added amount of raloxifene hydrochloride was dissolved
 shown by the presence of solid material at the bottom of the vessel and essen-
 tially no colouring of the fluid.

25

A similar dissolution test was performed using 60 mg raloxifene hy-
 drochloride in 0.1 M phosphoric acid. In this case all raloxifene hydrochloride
 seemed to be dissolved indicated by the absence of solids on the bottom of the

vessel and a strong yellow colouring of the fluid in the vessel.

Example 9

5

Dissolution of raloxifene acid addition salts or solvates in dilute hydrochloric acid or phosphoric acid

Using same procedures as in example 6, Raloxifene succinate,
10 raloxifene DL-lactate hemihydrate, raloxifene L-lactate hemihydrate, raloxifene malonate and raloxifene sulphate (2-propanol solvate) were tested for dissolution in dilute hydrochloric acid or phosphorous acid.

All these tests showed complete dissolution shown be absence of sol-
15 ids in the vessel and strong colouring of the liquid.

C L A I M S

1. Raloxifene acid addition salt or solvate thereof being raloxifene succinate in crystalline form having the following X-ray crystallographic positions:

XRD:

	<u>D</u>	<u>2Theta</u>	<u>I(rel)</u>	<u>I(abs)</u>	<u>FWHM</u>
10	13.195230	6.6933	20.78	8475	0.1400
	9.695642	9.1137	13.43	5476	0.0300
	9.304945	9.4972	18.19	7419	0.1300
	8.394523	10.5300	13.26	5407	0.1000
15	7.944460	11.1283	14.15	5768	0.1000
	7.708667	11.4699	17.61	7180	0.1200
	7.526675	11.7482	12.32	5023	0.0898
	7.323294	12.0756	15.22	6205	0.1000
	7.160495	12.3512	13.04	5316	0.0800
20	6.926815	12.7696	23.68	9655	0.1300
	6.606409	13.3917	29.08	11856	0.1400
	6.463392	13.3894	14.45	5891	0.0898
	6.285432	14.0789	21.24	8662	0.1200
	6.127742	14.4432	63.63	25947	0.1200
25	5.961999	14.8469	15.55	6342	0.0900
	5.875574	15.0665	15.77	6430	0.0898
	5.788967	15.2933	16.15	6585	0.1400
	5.624221	15.7441	34.74	14167	0.1200
	5.453763	16.2394	22.89	9334	0.1300
30	5.276560	16.7887	12.71	5182	0.1200
	5.095057	17.3913	14.19	5786	0.1100
	5.020392	17.6520	11.12	4535	0.0898
	4.835944	18.3309	18.30	7461	0.1200
	4.765096	18.6059	18.62	7591	0.1100

	4.630456	19.1519	65.88	26864	0.1600
	4.525518	19.6003	15.16	6180	0.0800
	4.484997	19.7792	24.48	9982	0.1000
	4.376528	20.2745	18.78	7659	0.1000
5	4.352225	20.3889	19.11	7790	0.1000
	4.227757	20.9959	29.39	11984	0.1000
	4.191265	21.1808	56.82	23171	0.0800
	4.158052	21.3520	40.16	16377	0.0898
	4.101947	21.6475	17.14	6988	0.0800
10	4.062068	21.8626	19.79	8072	0.1000
	4.010082	22.1496	11.70	4771	0.0600
	3.921660	22.6556	100.00	40776	0.1300
	3.860487	23.0194	29.04	11842	0.1100
	3.813566	23.3066	19.25	7850	0.1100
15	3.732687	23.8189	19.33	7884	0.1300
	3.694791	24.0669	22.47	9161	0.1100
	3.644300	24.4054	18.84	7680	0.1400
	3.544078	25.1067	13.63	5556	0.0700
	3.496160	25.4565	16.28	6637	0.0898
20	3.446458	25.8299	20.36	8300	0.2100
	3.398344	26.2021	12.35	5036	0.1200
	3.373032	26.4022	8.82	3597	0.0898
	3.305938	26.9481	14.08	5741	0.1100
	3.281940	27.1489	10.08	4112	0.0898
25	3.260437	27.3314	9.66	3937	0.0898
	3.227083	27.6194	19.22	7838	0.1200
	3.179256	28.0434	16.28	6640	0.2600
	3.146269	28.3435	8.89	3627	0.0898
	3.121159	28.5764	9.58	3907	0.0900
30	3.097691	28.7975	10.64	4337	0.0400
	3.074307	29.0213	19.64	8008	0.1200
	3.032262	29.4328	10.17	4148	0.1300
	3.010128	29.6541	9.43	3847	0.0898

2. Raloxifene acid addition salt or solvate thereof being raloxifene sulphate 2-propanol solvate.

3. Raloxifene acid addition salt or solvate thereof according to claim 2, wherein raloxifene sulphate 2-propanol solvate is in crystalline form having the
5 following X-ray crystallographic positions:

XRD:

	D	2Theta	I(rel)	I(abs)	FWHM
10	14.374007	6.1439	26.57	5009	0.0900
	10.303750	8.5748	29.62	5583	0.1300
	9.201529	9.6042	26.22	4942	0.1100
15	8.871726	9.9621	29.84	5624	0.1300
	8.569965	10.3138	22.25	4195	0.0400
	8.320378	10.6241	25.97	4896	0.1200
	7.945119	11.1274	38.65	7286	0.1300
	7.514174	11.7678	20.56	3876	0.1041
20	7.205108	12.2745	25.04	4721	0.1400
	6.537437	13.5336	66.78	12590	0.1400
	6.228787	14.2076	21.88	4126	0.1100
	5.628329	15.7325	20.71	3904	0.0900
	5.540447	15.9837	27.40	5166	0.1100
25	5.322476	16.5489	64.98	12249	0.1500
	5.138694	17.2425	21.65	4082	0.1100
	5.020317	17.6522	64.05	12074	0.1400
	4.706881	18.8381	100.00	18851	0.1300
	4.618097	19.2036	60.47	11400	0.0800
30	4.538129	19.5453	59.35	11189	0.1100
	4.471816	19.8381	67.03	12636	0.1200
	4.261964	20.8255	54.78	10327	0.1100
	4.204757	21.1121	51.35	9680	0.1600
	4.156029	21.3625	46.65	8794	0.1041

	4.093305	21.6938	25.93	4888	0.0900
	4.035960	22.0058	24.21	4563	0.1800
	3.937182	22.5651	25.37	4784	0.1200
	3.835400	23.1721	22.17	4179	0.0900
5	3.796528	23.4127	40.94	7718	0.0900
	3.767170	23.5978	61.03	11505	0.1100
	3.691303	24.0899	20.10	3790	0.1500
	3.639317	24.4393	47.20	8897	0.1200
	3.590489	24.7769	28.23	5321	0.1600
10	3.511060	25.3467	29.66	5592	0.1100
	3.478586	25.5873	23.70	4468	0.1041
	3.416539	26.0601	37.38	7047	0.1900
	3.355389	26.5436	20.28	3823	0.1300
	3.314637	26.8760	17.08	3220	0.1200
15	3.271015	27.2413	15.24	2874	0.0600
	3.252583	27.3987	14.71	2773	0.1041
	3.100446	28.7714	23.04	4344	0.1200
	3.079703	28.9694	19.73	3720	0.1041
	3.033828	29.4172	29.23	5511	0.1300
20	3.009744	29.6580	15.28	2880	0.1041
	2.937725	30.4024	13.30	2507	0.1700

4. Raloxifene acid addition salt of solvate thereof being raloxifene malonate in crystalline form having the following X-ray crystalline positions:

25

XRD:

	<u>D</u>	<u>2Theta</u>	<u>I(rel)</u>	<u>I(abs)</u>	<u>FWHM</u>
30	14.385166	6.1391	36.51	6471	0.0100
	13.125024	6.7292	38.91	6896	0.1300
	10.305386	8.5734	37.32	6614	0.1700
	9.279238	9.5236	39.85	7062	0.1300

	8.860721	9.9745	34.60	6133	0.0900
	8.510328	10.3863	33.27	5895	0.0900
	8.314361	10.6318	33.02	5852	0.0800
	7.947949	11.1234	41.61	7375	0.1600
5	7.265135	12.1727	35.79	6343	0.1300
	6.882996	12.8512	29.65	5254	0.0300
	6.537915	13.5326	60.19	10667	0.1800
	6.258251	14.1404	61.12	10833	0.2100
	6.003203	14.7444	31.92	5657	0.1200
10	5.877911	15.0605	29.17	5170	0.0600
	5.794580	15.2784	29.33	5198	0.0200
	5.663226	15.6349	49.63	8796	0.1300
	5.550457	15.9547	36.61	6487	0.0800
	5.354103	16.5438	55.84	9897	0.2200
15	5.134028	17.2583	30.18	5349	0.1378
	5.023848	17.6397	55.21	9784	0.2100
	4.836637	18.3283	36.13	6404	0.1400
	4.700761	18.8628	71.64	12696	0.1600
	4.644808	19.0922	86.46	15323	0.1500
20	4.538522	19.5436	61.36	10874	0.1300
	4.472256	19.8361	50.40	8931	0.1000
	4.347111	20.4132	37.86	6709	0.1000
	4.247918	20.8951	88.12	15616	0.2300
	4.161428	21.3344	73.93	13101	0.1600
25	4.085803	21.7341	37.19	6591	0.1100
	4.019584	22.0966	35.60	6309	0.1500
	3.921695	22.6554	100.00	17722	0.1700
	3.765729	23.6059	50.70	8986	0.2000
	3.703455	24.0097	34.79	6166	0.1200
30	3.638542	24.4446	47.30	8382	0.1900
	3.499221	25.4339	44.29	7849	0.2000
	3.426872	25.9801	43.63	7732	0.2200
	3.292398	27.0610	23.39	4145	0.1000
	3.253755	27.3886	25.03	4435	0.1400

3.192249	27.9269	22.18	3931	0.1400
3.094846	28.8246	28.68	5083	0.3000
3.034329	29.4123	27.30	4338	0.1900

5 5. Raloxifene acid addition salt or solvate thereof wherein the
raloxifene acid addition salt of solvate thereof is selected among: raloxifene D-
lactate, raloxifene L-lactate, Raloxifene DL-lactate, raloxifene D-lactate hemi-
hydrate, raloxifene D-lactate $\frac{1}{4}$ -hydrate, raloxifene L-lactate hemihydrate,
raloxifene L-lactate $\frac{1}{4}$ -hydrate, raloxifene DL-lactate hemihydrate and raloxifene
10 DL-lactate $\frac{1}{4}$ -hydrate.

6. Raloxifene acid addition salt or solvate thereof according to claim 5,
wherein the raloxifene acid addition salt or solvate thereof is raloxifene L-lactate
hemihydrate being in crystalline form having the following X-ray crystalline po-
sitions:

15

XRD:

	D	2Theta	I(rel)	I(abs)	FWHM
20	14.639874	6.0322	17.56	6122	0.1200
	13.207421	6.6871	15.07	5254	0.1200
	10.875932	8.1229	80.41	28029	0.1200
	9.268456	9.5347	22.67	7903	0.1200
	8.140638	10.8593	17.92	6247	0.1200
25	7.488503	11.8083	15.59	5433	0.1000
	7.310331	12.0971	12.47	4347	0.0800
	7.089508	12.4754	25.79	8991	0.1000
	6.931874	12.7603	12.78	4454	0.0900
	6.723932	13.1566	27.83	9701	0.1300
30	6.551458	13.5045	14.20	4949	0.0900
	6.359432	13.9143	30.57	10656	0.1100
	6.130010	14.4378	21.33	7435	0.1300
	5.853018	15.1249	36.40	12687	0.1100
	5.626204	15.7385	15.49	5401	0.1300

	5.507643	16.0795	23.25	8106	0.1000
	5.447238	16.2590	13.21	4606	0.0870
	5.224449	16.9573	19.21	6697	0.1100
	5.160516	17.1690	17.10	5961	0.0870
5	5.083475	17.4312	14.74	5137	0.1100
	4.954247	17.8896	19.64	6848	0.1000
	4.863750	18.2252	28.34	9879	0.0800
	4.805168	18.4494	46.26	16125	0.0700
	4.756883	18.6383	49.99	17425	0.0800
10	4.656926	19.0420	19.10	6659	0.1900
	4.630194	19.1530	17.96	6260	0.0870
	4.566015	19.4248	21.34	7438	0.1000
	4.487514	19.7680	12.76	4447	0.1000
	4.347753	20.4101	11.69	4074	0.1100
15	4.301465	20.6322	19.17	6682	0.0900
	4.224555	21.0120	14.55	5072	0.0870
	4.186561	21.2049	23.33	8134	0.1700
	4.065767	21.8425	26.06	9084	0.1000
	4.015560	22.1190	17.10	5929	0.1000
20	3.976949	22.3365	14.98	5223	0.0500
	3.935785	22.5732	34.50	12028	0.1100
	3.867038	22.9799	100.00	34859	0.1000
	3.779481	23.5198	40.14	13991	0.0800
	3.742319	23.7567	59.68	20805	0.1000
25	3.710418	23.9640	13.17	4591	0.0870
	3.645564	24.3968	11.19	3902	0.0800
	3.621808	24.5593	18.71	6524	0.1000
	3.552536	25.0459	16.01	5581	0.1000
	3.516088	25.3098	13.46	4691	0.0600
30	3.498357	25.4402	12.66	4413	0.0700
	3.467075	25.6737	10.74	3745	0.0500
	3.418947	26.0414	21.49	7491	0.1000
	3.395298	26.2260	12.12	4225	0.0870
	3.369948	26.4268	15.48	5369	0.0700

	3.358554	26.5181	14.33	4995	0.0600
	3.244985	27.4641	11.90	4149	0.0700
	3.229427	27.5990	9.63	3356	0.0870
	3.177657	28.0578	15.07	5253	0.1200
5	3.144884	28.3562	32.65	11381	0.1000
	3.106130	28.7176	9.83	3425	0.0800
	3.082970	28.9380	9.00	3138	0.0870
	3.056106	29.1980	8.56	2984	0.0870
	3.032184	29.4335	8.74	3048	0.1100
10	2.994539	29.8121	8.27	2884	0.0700
	2.979114	29.9700	9.26	3229	0.0800
	2.924922	30.5387	9.19	3203	0.1800
	2.870290	31.1346	16.32	5689	0.1400
	2.828902	31.6019	13.59	4737	0.1100
15	2.762611	32.3808	10.83	3775	0.1000

7. Raloxifene acid addition salt or solvate thereof according to claim 5,
 wherein the raloxifene acid addition salt or solvate thereof is raloxifene L-lactate
 ¼-hydrate being in crystalline form having the following X-ray crystalline posi-
 tions:

XRD:

	D	2Theta	I(rel)	I(abs)	FWHM
25	14.079244	6.2726	45.93	16568	0.1300
	9.974912	8.8580	32.43	11699	0.1100
	9.526523	9.2758	71.31	25721	0.1200
	8.215598	10.7600	47.82	17248	0.1100
30	7.246270	12.2045	80.04	28871	0.1100
	7.065557	12.5178	16.17	5832	0.0700
	6.878001	12.8606	22.74	8201	0.1200
	6.283709	14.0828	66.27	23901	0.0800
	6.194698	14.2862	53.98	19470	0.0984

	5.859529	15.1080	11.17	4028	0.0984
	5.744935	15.4112	16.16	5828	0.1200
	5.312222	16.6751	18.02	6499	0.1200
	5.046910	17.5585	34.26	12356	0.0900
5	4.978933	17.8001	54.66	19715	0.1000
	4.918535	18.0205	17.40	6277	0.0984
	4.746264	18.6804	26.77	9655	0.1000
	4.712771	18.8143	46.35	16716	0.0900
	4.569429	19.4101	57.60	20777	0.1000
10	4.455985	19.9093	53.60	19332	0.1200
	4.345589	20.4204	12.70	4579	0.0900
	4.268096	20.7952	86.33	31139	0.0900
	4.106332	21.6241	20.17	7274	0.1100
	4.042283	21.9710	22.73	8197	0.1200
15	3.944656	22.5218	23.46	8462	0.1000
	3.913129	22.7056	100.00	36069	0.1100
	3.831706	23.1947	15.49	5586	0.0900
	3.777075	23.5350	69.72	25148	0.1400
	3.735872	23.7983	14.85	5358	0.0984
20	3.667856	24.2463	11.94	4305	0.0900
	3.639035	24.4413	13.87	5001	0.0800
	3.589918	24.7809	9.38	3383	0.0984
	3.545715	25.0949	23.58	8505	0.0800
	3.505655	25.3864	33.63	12131	0.1100
25	3.442223	25.8622	22.60	8152	0.1100
	3.411017	26.1030	10.82	3901	0.0984
	3.371851	26.4117	44.16	5108	0.1000
	3.280618	27.1600	15.23	5494	0.1100
	3.251104	27.4114	14.23	5134	0.0800
30	3.232072	27.5760	19.25	6943	0.1100
	3.153056	28.2812	12.42	4479	0.1900
	3.143130	28.3724	12.29	4432	0.0984
	3.081939	28.9479	17.16	6189	0.2200
	3.040378	29.3524	9.73	3510	0.1300

	2.990508	29.8532	15.29	5514	0.1400
	2.929711	30.4876	11.37	4102	0.1200
	2.892397	30.8906	18.91	6822	0.1200
	2.856192	31.2922	8.91	3214	0.1100
5	2.818108	31.7261	14.79	5336	0.2500
	2.765584	32.3450	15.86	5720	0.1300

8. Raloxifene acid addition salt or solvate thereof according to claim 5,
 wherein the raloxifene acid addition salt or solvate thereof is raloxifene DL-
 10 lactate hemihydrate being in crystalline form having the following X-ray crystal-
 line positions:

XRD:

15	D	2Theta	I(rel)	I(abs)	FWHM
	13.595814	6.4959	28.40	12683	0.1400
	10.855533	8.1382	16.15	7211	0.1200
	9.849394	8.9711	32.17	14369	0.1000
20	9.534325	9.2682	66.95	29898	0.1300
	8.150249	10.8465	45.20	20188	0.1300
	7.240730	12.2138	63.53	28374	0.1400
	6.769843	13.0670	18.42	8227	0.1500
	6.272666	14.1077	75.67	33794	0.1900
25	5.818832	15.2143	13.28	5933	0.2000
	5.657337	15.6513	18.07	8070	0.1300
	5.505030	16.0872	10.51	4692	0.1000
	5.261933	16.8357	17.48	7806	0.1400
	5.089504	17.4104	16.14	7210	0.1000
30	5.001569	17.7189	41.94	18732	0.0900
	4.958950	17.8725	29.16	13023	0.1148
	4.797388	18.4795	19.39	8660	0.1100
	4.669322	18.9910	49.20	21972	0.1400
	4.574684	19.3876	63.21	28227	0.1000

	4.533019	19.5676	44.94	20071	0.1148
	4.440548	19.9792	32.70	14604	0.1200
	4.301886	20.6301	100.00	44659	0.1500
	4.155406	21.3657	78.00	34833	0.1600
5	4.059049	21.8797	27.53	12296	0.1800
	3.960846	22.4285	25.59	11427	0.1000
	3.907408	22.7393	83.48	37282	0.1200
	3.865461	22.9894	16.46	7350	0.1148
	3.828892	23.2120	17.46	7798	0.0900
10	3.773130	23.5599	50.71	22649	0.1200
	3.716486	23.9243	23.06	10300	0.1300
	3.652238	24.3515	15.79	7053	0.1800
	3.584725	24.8174	12.91	5764	0.1500
	3.486791	25.5261	30.45	13600	0.1200
15	3.439149	25.8858	22.21	9919	0.1300
	3.396267	26.2184	17.86	7978	0.1100
	3.370045	26.4261	12.48	5572	0.1148
	3.329320	26.7553	9.21	4113	0.1100
	3.292728	27.0582	11.81	5274	0.1000
20	3.278070	27.1815	11.25	5026	0.1148
	3.218620	27.6935	21.24	9485	0.1900
	3.167986	28.1452	13.80	6162	0.0900
	3.143230	28.3715	30.33	13546	0.1000
	3.095423	28.9191	14.02	6260	0.1200
25	3.024921	29.5058	11.56	5161	0.1400
	3.007253	29.6831	13.40	5984	0.1300

9. Use of a raloxifene acid addition salt or solvate thereof according to any of claims 1-8, for the manufacture of a pharmaceutical composition capable of fast and reliable release of the raloxifene acid addition salt or solvate thereof in gastric juice.

10. Use according to claim 9, where the pharmaceutical composition is intended for the treatment of cancer or osteoporosis, or for inhibiting cartilage degradation.

11. Pharmaceutical composition capable of fast and reliable release of the active ingredients in gastric juice, comprising a raloxifene acid addition salt or solvate thereof according to any of claims 1-8.

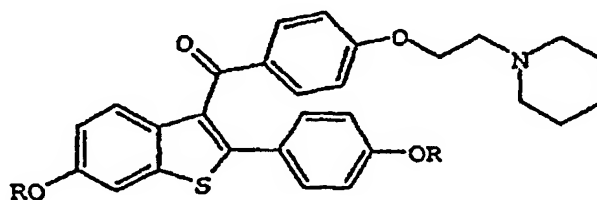
12. Pharmaceutical composition according to claim 11, wherein the pharmaceutical is intended for the treatment of cancer or osteoporosis, or for inhibiting cartilage degradation.

13. Process for the manufacture of raloxifene lactate comprising the following steps:

to a solution of the compound having the general formula I in an sol-

10 vent

15



Formula I

20 wherein R represent two independently selected hydroxyl protection groups,

is added a suitable reagent to remove the protection groups;

lactic acid is added to the mixture, and

raloxifene lactate is precipitated from the mixture and isolated.

25 14. Process according to claim 13, wherein the groups R are independently selected from: C₁-C₄ alkyl, C₅-C₇ cycloalkyl, benzyl -COR² or SO₂R², wherein R² is C₁-C₄ primary or secondary alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ chloroalkyl, C₁-C₄ alkylphenyl, C₁-C₄ alkoxyphenyl, mono- or dinitrophenyl or mono- or di(chloro or fluoro)phenyl.

30 15. Process according to claim 13 or 14, wherein the two R groups are identical.

16. Process according to claim 13-15, wherein the solvent is selected from alcohols having 1 to 5 carbon atoms.

17. Process according to claim 16, wherein the alcohol is a monovalent

alcohol.

18. Process according to claim 17, wherein the alcohol is ethanol.

19. Process according to claim 18, wherein the alcohol is 96% ethanol.

20. Process according to any of claim 13 to 19, wherein the lactate is

5 L-lactate.

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30/09/02

Novel raloxifene acid addition salts and/or solvates thereof, improved method
5 for purification of said raloxifene acid addition salts and/or solvates thereof and
pharmaceutical compositions comprising these.

A B S T R A C T

10

Raloxifene acid addition salts or solvates thereof, having improved dissolution
properties in media comprising hydrogen chloride are described, compared with
similar preparations based on raloxifene or raloxifene hydrochloride. The dis-
closed acid addition salts or solvates thereof show an improved dissolubility in
15 media comprising hydrochloric acid, such as the gastric juice. The acid addition
salts or solvates thereof are addition salts or solvates of raloxifene and a phar-
maceutical acceptable acid selected among succinic acid, lactic acid, malonic
acid or sulphuric acid. Further, crystalline forms of the raloxifene salts and sol-
vates thereof are disclosed.

20 The raloxifene acid addition salts and/or solvates thereof are useful for the
preparation of pharmaceutical composition for oral administration capable of
fast and reliable release of the active ingredients in the stomach of the patient, in
particular for the treatment of cancer or osteoporosis, or for inhibiting cartilage
degradation.

25 A new method for preparation of raloxifene lactate is also disclosed.

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Figure 1

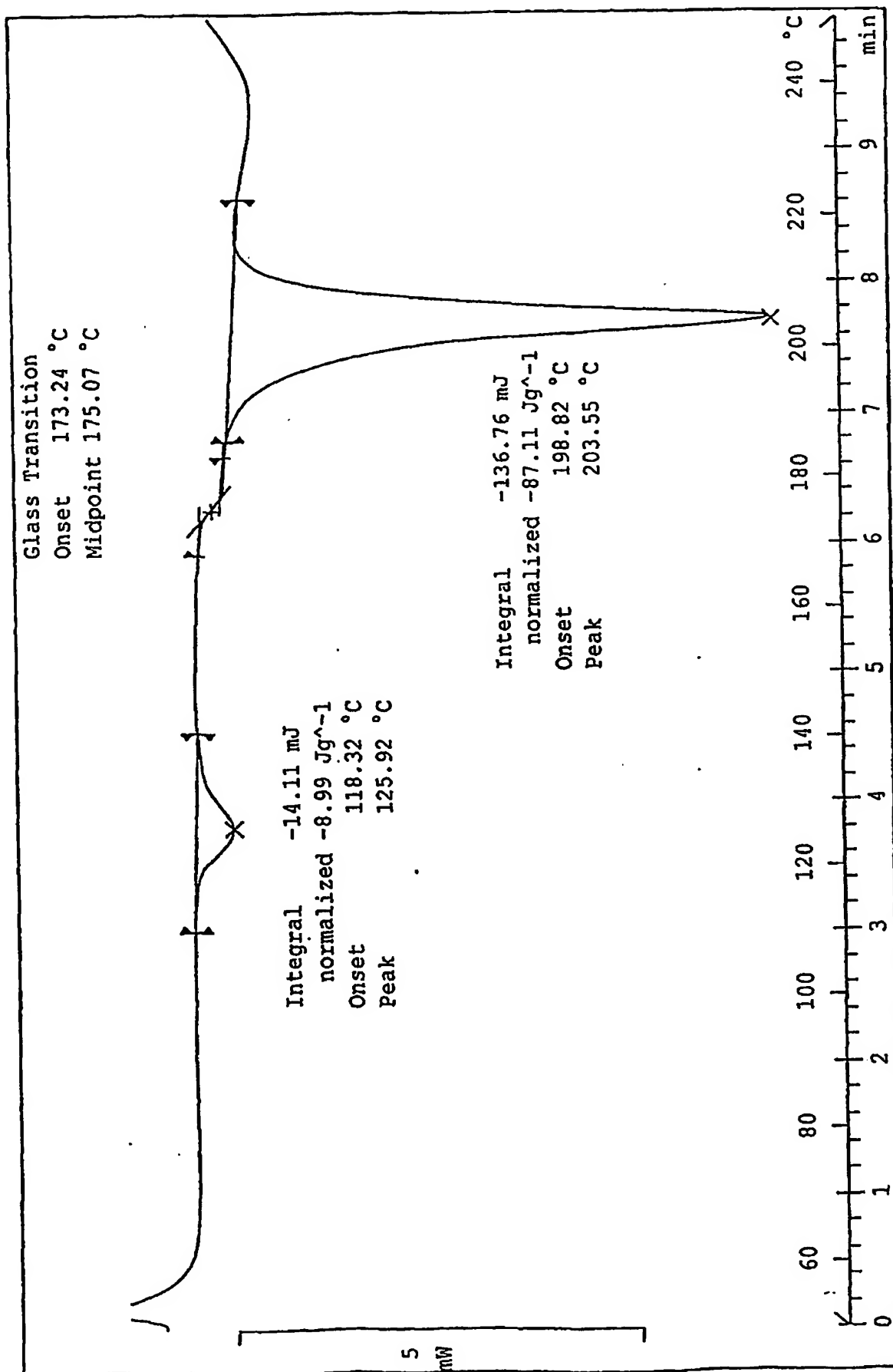
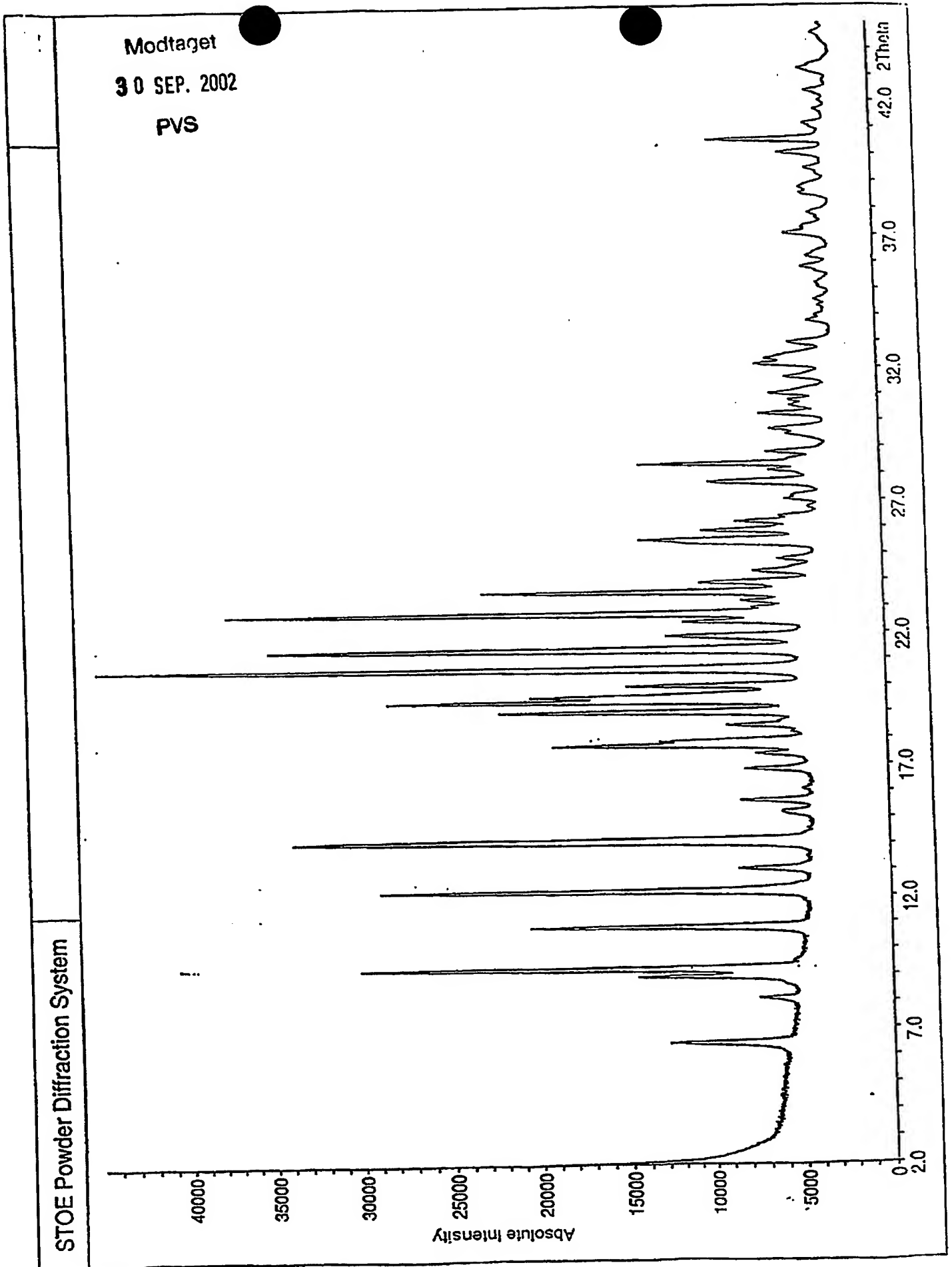


Figure 2



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Figure 3

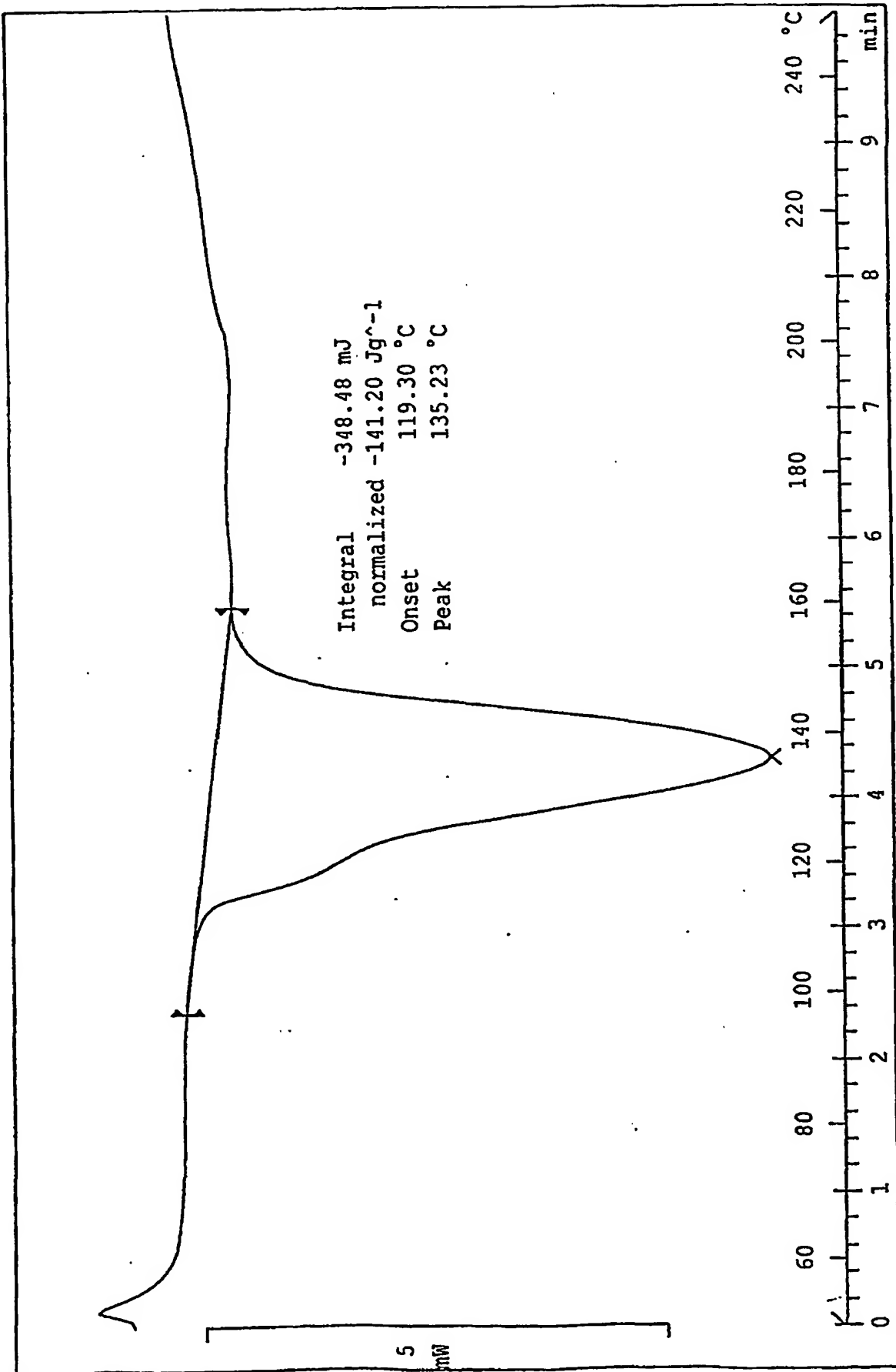


Figure 4

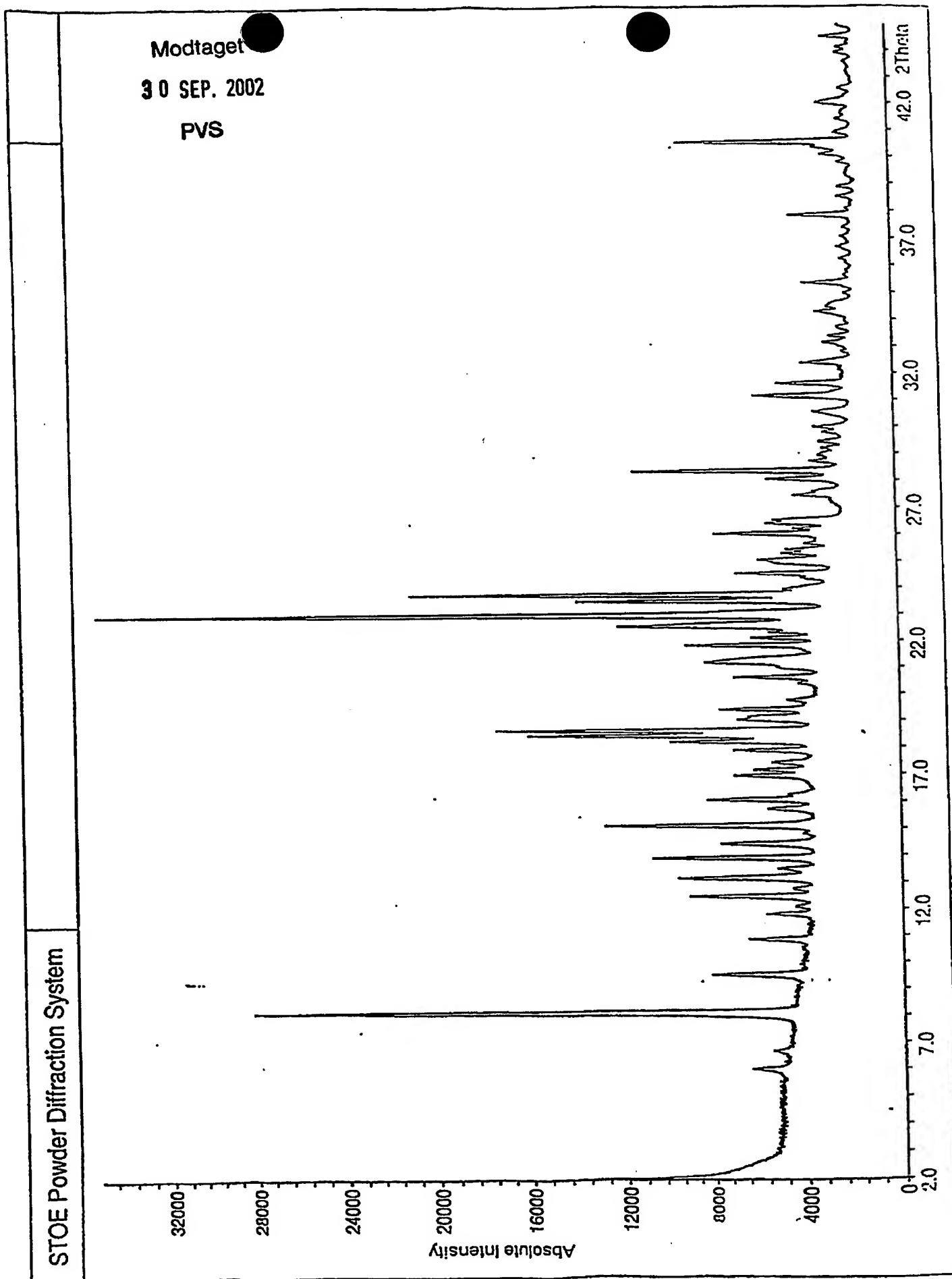


Figure 5

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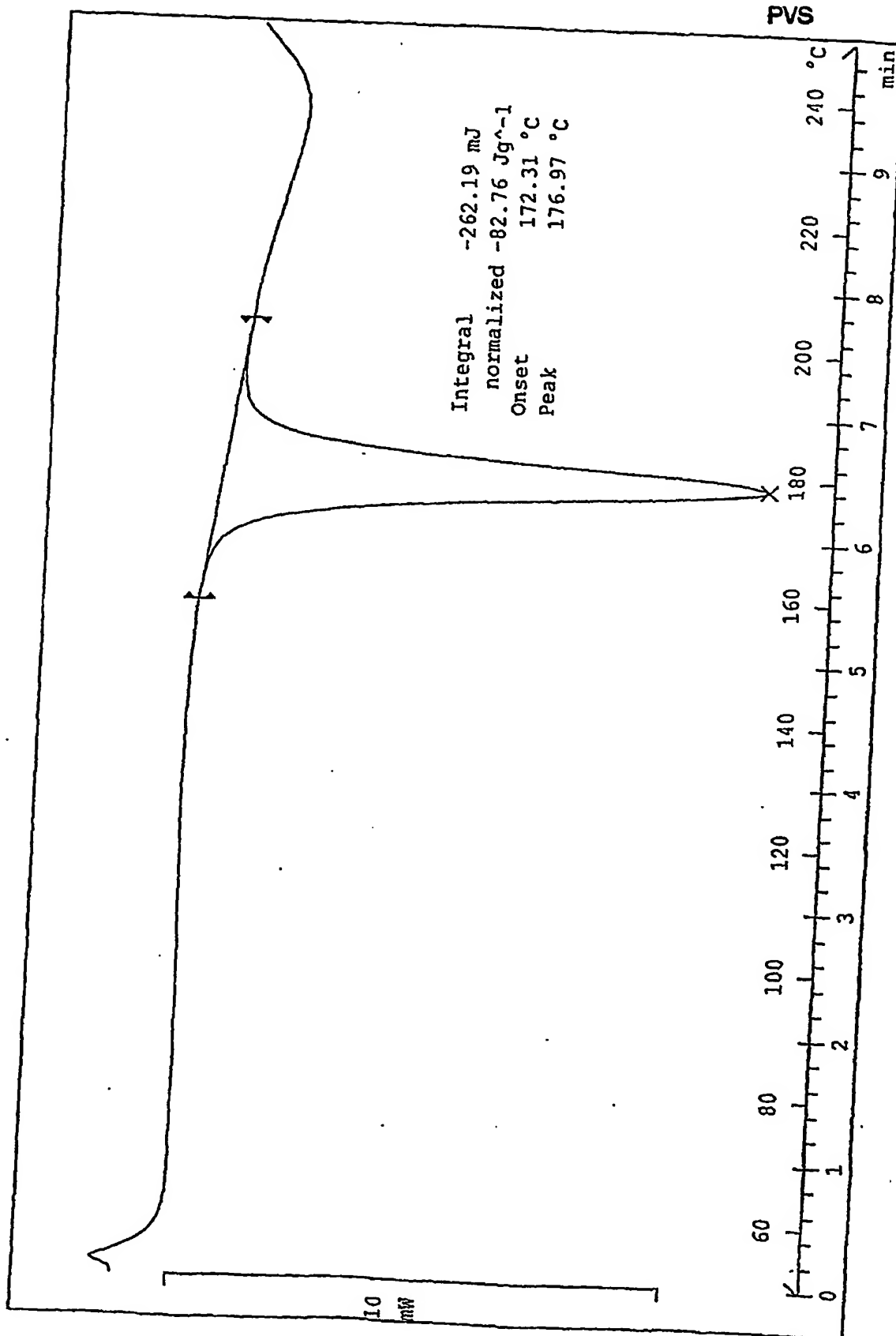
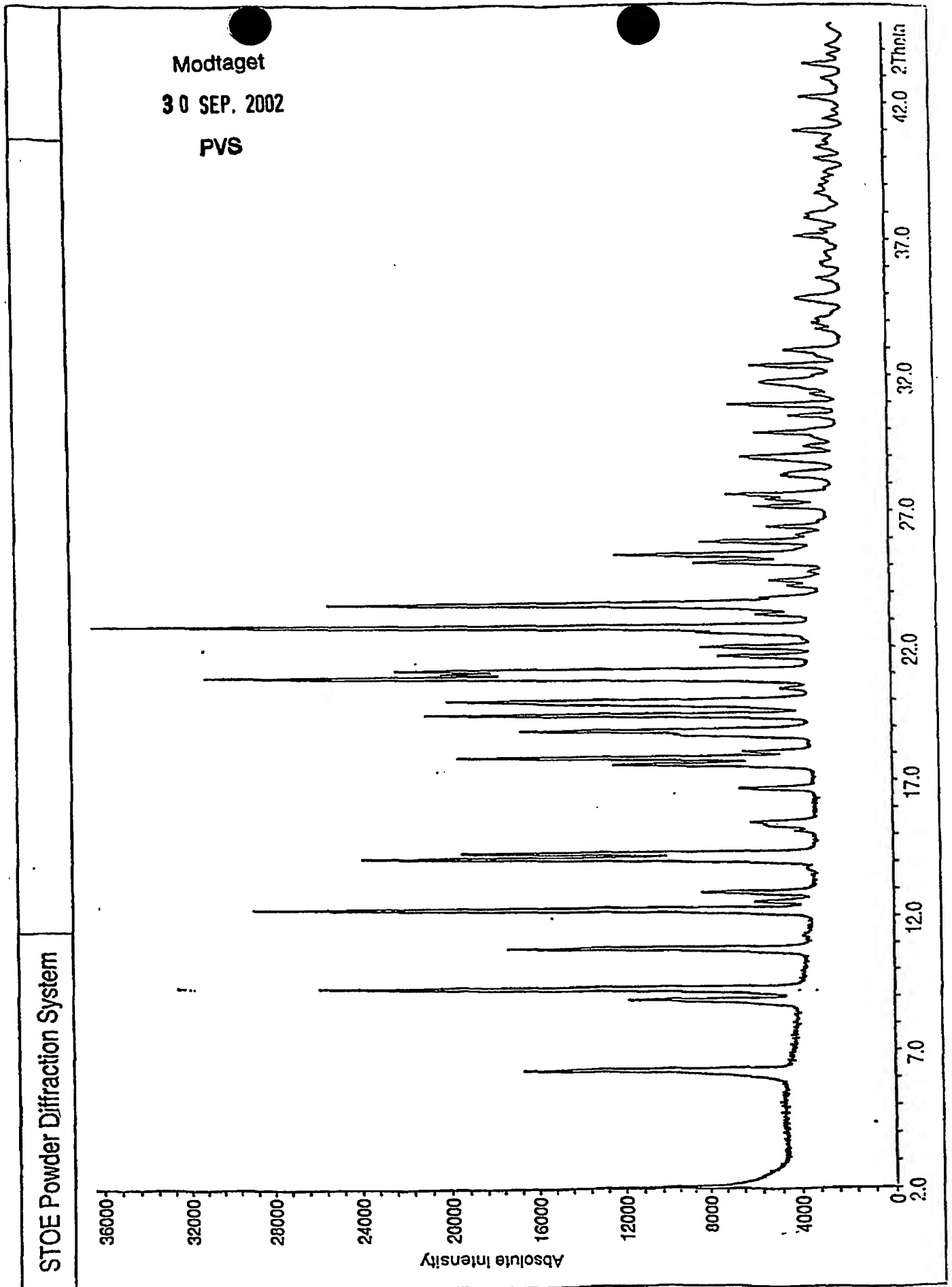


Figure 6



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